



Mediastinal granulomatous reaction in lung cancer in cappadocia region

Kapadokya bölgesinde akciğer kanserlerinde mediastinal granülatöz reaksiyon

Mediastinal granulomatous reaction in lung cancer

Omer Faruk Demir, Omer Onal
Department of Thoracic Surgery, Faculty of Medicine, University of Erciyes, Kayseri, Turkey

Öz

Amaç: Bu çalışmanın amacı kapadokya bölgesinde akciğer kanseri nedeniyle cerrahi uygulanan hastalarda invaziv evreleme sırasında mediastinal granülatöz reaksiyonları araştırmaktır. **Gereç ve Yöntem:** Kapadokya bölgesinde 2003 ile 2016 yılları arasında akciğer kanseri nedeniyle cerrahi tedavi uygulanan 469 hasta çalışmaya dahil edildi. Hastaların invaziv evreleme sırasında mediastinoskopi ve torakotomi ile örneklenen lenf nodları değerlendirildi. **Bulgular:** 469 hastadan mediastinoskopi ve torakotomi ile toplam 2637 lenf nodu (ortalama:5,6) istasyonu örneklendi. 21 (4.4%) hastada granülatöz reaksiyon tespit edildi. Sırası ile erkek ve kadın hasta sayısı 17 ve 4 idi. Hastaların yaşları 52 ile 73 (mean: 62.19 ± 7.5) arasında değişiyordu. Granülatöz reaksiyonlu hastalarda en yaygın kanser tipi squamöz kanserlerdi. Diğer yaygın kanserler adeno kanserler ve large cell kanserlerdi. Sarkoid reaksiyon ve metastatik lenf nodu iki hastada tespit edildi. **Tartışma:** Kapadokya bölgesinde akciğer kanseri için granülatöz reaksiyon oranı 4.4% dır. Granülatöz reaksiyon erken evrelerde daha sık görülmesine karşın, ileri evre hastalarda görülebilir ve metastatik lenf nodlarına eşlik edebilir.

Anahtar Kelimeler

Granülatöz Reaksiyon; İnvaziv Evreleme; Akciğer Kanseri

Abstract

Aim: This study aims to investigate the mediastinal granulomatous reactions detected during invasive staging in patients undergoing surgical treatment due to lung cancer in Cappadocia region. **Material and Method:** 469 patients were included in the study who underwent surgical treatment for lung cancer between 2003 and 2016 in Cappadocia region. Lymph node stations sampled by mediastinoscopy and thoracotomy were evaluated during the invasive staging of the patients. **Results:** A total of 2637 (mean: 5.6) lymph node stations were sampled from 469 patients with mediastinoscopy and thoracotomy. 21 (4.4%) patients had a granulomatous reaction. The numbers of male and female patients were 17 and 4, respectively. The age of the patients ranged from 52 to 73 years (mean 62.19 ± 7.5). It was determined that the most common type of cancer in patients with granulomatous reactions were squamous carcinoma (n = 9). Other common cancers were adenocarcinoma (n = 7) and large cell (n = 2) carcinoma. Lymph node metastasis and sarcoidosis reaction association were found in two patients. **Discussion:** The frequency of granulomatous reactions for lung cancer is 4.4% in Cappadocia region. Although the granulomatous reaction is more frequent in early stage disease, it may be seen in advanced stage patients and may accompany metastatic lymph nodes.

Keywords

Granulomatous Reaction; Invasive Staging; Lung Cancer

DOI: 10.4328/JCAM.5415

Received: 03.10.2017 Accepted: 20.10.2017 Printed: 01.11.2017 J Clin Anal Med 2017;8(6): 541-4

Corresponding Author: Omer Faruk Demir, Department of Thoracic Surgery, Erciyes University Medical Faculty, 38039, Kayseri, Turkey.

T.: +90 3522076666 GSM: +905302935204 F.: +90 3524375273 E-Mail: ofdemir@erciyes.edu.tr

Introduction

Non-small cell lung cancer (NSCLC) is among the most common cancers today and is responsible for 75% to 80% of all cancer-related deaths [1-2]. Mediastinal lymph node metastasis for non-small cell lung cancer is both an important prognostic factor and a very important determinant in the planning of treatment. Therefore, the right mediastinal lymph node staging is the basis for determining the optimal treatment of NSCLC [3]. Granulomatous reactions located in the mediastinal area of the lung parenchyma cause confusion in diagnosis and treatment and affect the methods used in the evaluation of various patients such as PET CT (Positron Emission Tomography) and cause fault results [4]. In fact, granulomatous reactions are a series of diseases characterized by granuloma formation, contain many diseases such as vasculitis, immunologic disorders, infections, leukocyte oxidase defects, hypersensitivity, and neoplasm, and they might also be formed due to drugs [5]. This type of granuloma formation is found in many types of cancer, including lung cancers, and although actual cause of it is not clear, it is thought to be due to T cell mediated immunological mechanisms [6]. Granulomatous reactions are regarded as a sarcoid reaction or sarcoid-like lymphadenopathy when it is seen with neoplastic diseases [7].

This study aims to evaluate the incidence of granulomatous reactions in patients with lung cancer in Cappadocia region.

Material and Method

Patients who underwent surgical treatment for lung cancer in our clinic between 2003 and 2016 were retrospectively investigated. Patients with granulomatous disease, chemoradiotherapy, synchronous and metachronous cancer were excluded from the study. 469 patients with lung cancer who underwent mediastinoscopy and surgical treatment for NSCLC were enrolled in the study. Pathology results of all lymph nodes removed during mediastinoscopy and thoracotomy were evaluated. Age, gender, type of resection, cancer type, localization, tumor size and histopathological diagnosis of the patients were obtained. Surgical staging of the patients was done according to the 7th lung cancer staging system.

Statistical Method

IBM SPSS 21.0 software was used for data analysis. Average, standard deviation, ratio, and frequency values were used for the descriptive statistics of the data in the study. The significance of differences in a group was analyzed by the Fisher's exact test. Spearman's analysis was used for correlation.

Results

A total of 2637 (mean 5.6) regional lymph node stations were sampled during cervical video-mediastinoscopy and thoracotomy in 469 patients. 428 (91.3%) of the patients were male, and 41 (8.7%) were female. The characteristics of all patients are summarized in the table1.

Granulomatous reactions were detected in 33 of 2637 lymph node stations (21 patients). The age range of the patient group with granulomatous reaction was found to be 52 to 73, and the mean age was 62.19 ± 7.5. Seventeen of the patients were male, and four were female. It was observed that the

Table 1. Baseline characteristics of patients

	All patients	Percent %
Age	62.6±8.8	
Sex		
M	429	90.8
F	43	9.2
Histopathology		
Adenocarcinoman	126	26.9
Squamous	272	58
Large-cell	38	8.1
Others	33	7.0
Tumor size		
T1a	31	6.6
T1b	76	16.2
T2a	163	34.8
T2b	117	24.9
T3a	82	17.5
Stage		
1A	67	14.3
1B	106	22.6
2A	162	34.5
2B	116	24.7
3A	18	3.8
Surgery		
RUL	109	23.2
RML	7	1.5
RBL	16	3.4
RLL	95	20.3
RP	41	8.7
LUL	83	17.7
LLL	64	13.6
LP	54	11.5
Total patient	469	100

RUL: right upper lobectomy, RLL: right lower lobectomy, RBL: right bilobectomy,RML: right midle lobectomy, LUL: left upper lobectomy, LLL: left lower lobectomy, RP: right pneumonectomy, LP: left pneumonectomy.

distribution of the patients according to cancer histopathology was 9 of squamous carcinoma, 7 of adenocarcinoma, 2 of large-cell, 3 of others. One patient was T1a, 7 patients were T1b, 5 patients were T2a, 6 patients were T2b, and 2 patients were T3. Thirteen patients were determined as stage I, 6 patients were determined as stage II, and 2 patients were determined as stage III. The most common surgical procedure was right upper lobectomy (8 patients). This was followed by right lower lobectomy (4), left upper lobectomy (3), right bilobectomy (3), left lower lobectomy (1), right pneumonectomy (1), and left pneumonectomy (1). The characteristics of granulomatous reactions patients are summarized in table 2.

No correlation was detected with the granulomatous reaction in all parameters except stage. The results of the correlation test of patients with granulomatous reactions are summarized in the table 3. The frequency of incidental granulomatous reactions during invasive staging in patients undergoing surgical treatment for lung cancer is 4.4%. The granulomatous reaction is more frequent in stage I in patients with lung cancer (%7.5). Metastases were detected in the N1 lymph node in two patients with granulomatous reactions.

Table 2. Characteristics of granulomatous reaction patients

Age	Sex	Surgery	Histopathology	Tumor size	Stage	Lymph node
73	K	LLL	Oth	T2a	1B	2R-4R*-2L-6-7-9-11
59	E	RBL	Sq	T1b	1A	2R-4R-4L-8* - 11
53	E	LUL	Sq	T3	3A	2R*-4R*-2L*-7-5-9M
52	E	LUL	La	T2a	1B	2R*-4R-2L-4L-7-11
57	K	RBL	Oth	T1b	1A	4R-2L-4L-7* - 11
56	E	RP	Ad	T2b	2A	2R-4R-4L-7*- 8 - 9
72	E	RUL	Ad	T1b	1A	2R*-2L-4L-7*-8 - 10
63	E	RLL	Sq	T2b	2A	4R*-4L-7- 4 - 10
69	K	RUL	Ad	T2a	1B	2R-4R*-4L - 7* - 8 - 9
73	E	RLL	Sq	T2b	2A	2R-4R-4L-7*- 8 -10
72	E	RUL	Ad	T1b	1A	4R-2L-4L*-5-6-7*-10
54	E	LP	Sq	T3	3A	2R*-2L*-4L-6-7-11M
63	E	RLL	Sq	T2b	2A	2R-4R*-4L-9-10
59	K	RBL	Sq	T1b	1A	4R*-2L-4L-7
61	E	RUL	Sq	T1b	1A	2R-4R*-4L-7*-9-10
52	E	LUL	La	T2b	2A	2R-4R*-2L-4L-5-7-11
57	E	RUL	Oth	T1b	1A	2R*4R*-4L-9-10-11
56	E	RUL	Ad	T2b	2A	2R-4R-7*-11
65	E	RUL	Sq	T2a	1B	2R*-4R*-4L-7-8
72	E	RLL	Ad	T1a	1A	2R*-4R*-2L-4L-5-7
69	E	RUL	Ad	T2a	1B	2R-4R*-4L-7-11

RUL: right upper lobectomy, RLL: right lower lobectomy, RBL: right bilobectomy, RML: right middle lobectomy LUL: left upper lobectomy, LLL: left lower lobectomy, RP: right pneumonectomy, LP: left pneumonectomy, Sq: squamous cell carcinoma, Ad: adenocarcinoma, La: large cell carcinoma, Oth: other carcinoma, M: Metastatic lymph node, * : granulomatous reaction.

Table 3. Coleration between granulomatous reaction and other parameters

	Stage	Age	Sex	Histopathology	Tumor size	Surgery
r	-0.116	-0.016	0.009	0.006	-0.052	-0.082
Sarcoid reaction p	0.012	0.733	0.833	0.902	0.263	0.075

Spearman's rho coleration.
Coleration is significant at the 0.05 level.

Discussion

The granulomatous reaction in the lymph nodes is formed due to tumor necrosis, medical therapies, metastases, infections, and systemic diseases [7-9]. The granulomatous reaction is associated with many types of cancer [10-12]. There are different ratios in the literature regarding primary lung cancer and granulomatous reaction frequency, ranging from 1.3-4.3% [13-16]. We found that 4.4% of granulomatous reactions may be seen in the lymph nodes. Although the results of our study are compatible with some studies in the literature, the results are higher than those of the Japanese studies. We think that this situation happened because the incidence of the granulomatous disease is very low in Japan's geography. The rate of granulomatous reaction is higher in patients with lung cancer due to high incidence and prevalence of diseases associated with granulomatous lymphadenitis in our region. There are different opinions about whether age distribution is effective on the association of lung cancer and granulomatous reaction. In some studies, it has been claimed that there is no significant difference between patients with granulomatous and without granulomatous in terms of age distribution [13]. Some authors mention that associated with granulomatous

reaction and lung cancer in younger patients [14]. In our study, it was also found that age distribution was not significant in granulomatous reactions and lung cancer coexistence. In our study, there may not be any difference seen in terms of low average age of our patients because the patient group is composed of patients going to the ultimate surgery.

There are different views about the association of lung cancer and granulomatous reaction with cancer type. In some studies, it has been noted that the sarcoid reaction in lung cancer is related to squamous lung cancer [15,17]. In both studies, it was thought that exposure of the lymph nodes to the lymphatic drainage by the primary tumor suggests that the squamous cancer type grows more slowly than the other types. Tomimaru et al. reported that there is no relationship between cancer type and granulomatous reaction [13]. In this study, granulomatous reactions were most commonly seen in patients with squamous carcinoma. There was no relationship determined between cancer type and sarcoid reaction. We think that the association of granulomatous reaction with lung cancer varies depending on the dominance of lung carcinoma in the related geographical region.

Several authors mention that the granulomatous reaction is more frequent in early stage patients [13-15]. One of these authors reports a granulomatous reaction rate of 7.7% for stage 1 patients [15]. In this study, the association of granulomatous reaction and lung cancer was more frequent in the early stage of the disease in accordance with the literature. Granulomatous reactions distribution was 7.5% in stage-I patients. As a consequence, we determined that the incidence of granulomatous reactions was higher in early stage cancers. Lymph node metastasis was not seen in patients with lung cancer who had a granulomatous reaction in almost all previous studies [15,17,18]. In fact, this case was mentioned solely in 2 publications in the literature [13,19]. A case report conducted by Trisolini et al. showed a granulomatous reaction and metastatic lymph node involvement in a patient with stage 3A lung cancer [19]. Tomimaru et al. studied invasive staging in patients with lung cancer, detected metastatic lymph nodes in 4 of 22 patients with granulomatous reaction [13]. Three of these patients are stage 3. Similarly, in our region, metastatic lymph nodes were detected in 2 of 21 patients with granulomatous reaction. Both patients were stage 3A. It seems that the association of granulomatous lymphadenitis and metastatic lymph nodes can be detected in advanced stage disease.

Conclusion

The frequency of incidental sarcoid reactions during invasive staging in patients undergoing surgical treatment for lung cancer is 4.4% in Cappadocia region. We think that the association of granulomatous reaction and metastatic lymph nodes is more frequent and as the more studies are performed with the subject, this situation will be confirmed. Thereby, a broader prospective publication is needed about the subject.

Animal and Human Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding

The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors declare that they have no competing interest subject.

References

1. Tanaka F, Yanagihara K, Otake Y, Miyahara R, Kawano Y, Nakagawa T, et al. Surgery for non-small cell lung cancer: postoperative survival based on the revised tumor-node-metastasis classification and its time trend. *Eur J Cardiothorac Surg*. 2000; 18(2): 147–55.
2. Yoshimasu T, Kawago M, Hirai Y, Ohashi T, Tanaka Y, Oura S, et al. Fast Fourier Transform Analysis of Pulmonary Nodules on Computed Tomography Images from Patients with Lung Cancer. *Annals of Thoracic and Cardiovascular Surgery*. 2015; 21(1): 1–7.
3. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest*. 2009; 136(1): 260–71.
4. Kim BT, Lee KS, Shim SS, Choi JY, Kwon OJ, Kim H, et al. Stage T1 non-small cell lung cancer: preoperative mediastinal nodal staging with integrated FDG PET/CT—a prospective study. *Radiology*. 2006; 241(2): 501–9.
5. James DG. A clinicopathological classification of granulomatous disorders. *Postgraduate Medical Journal*. 2000; 76(897): 457–65.
6. Kurata A, Terado Y, Schulz A, Fujioka Y, Franke FE. Inflammatory cells in the formation of tumor-related sarcoid reactions. *Hum Pathol*. 2005; 36(5): 546–54.
7. Lai AT, Lam CM, Ng KK, Yeung C, Ho WL, Poon LT, et al. Hepatic actinomycosis presenting as a liver tumour: case report and literature review. *Asian Journal of Surgery*. 2004; 27(4): 345–7.
8. Lombart A, Escudero JM. The incidence and significance of epithelioid and sarcoid-like cellular reaction in the stromata of malignant tumours. A morphological and experimental study. *Eur J Cancer*. 1970; 6(6): 545–51.
9. Gregorie HB, Othersen HB, Moore MP. The significance of sarcoid-like lesions in association with malignant neoplasms. *Am J Surg*. 1962; 104(4): 577–86.
10. Brincker H. Sarcoid reactions in malignant tumours. *Cancer Treat Rev*. 1986; 13(3): 147–56.
11. Ouellet S, Albadine R, Sabbagh R. Renal cell carcinoma associated with peritumoral sarcoid-like reaction without intratumoral granuloma. *Diagnostic pathology*. 2012; 7(1): 28.
12. Wei H, Hou J, Pan J, Su X, Li L, Wang X, et al. A sarcoidosis-like granuloma reaction in the lymph nodes of a patient with lung squamous cancer: from stasis to the invasive phase with FGF1 gene amplification. *The clinical respiratory journal*. 2016; 10(4): 530–4.
13. Tomimaru Y, Higashiyama M, Okami J, Oda K, Takami K, Kodoma K, et al. Surgical results of lung cancer with sarcoid reaction in regional lymph nodes. *Jpn J Clin Oncol*. 2007; 37(2): 90–5.
14. Kamiyoshihara M, Hirai T, Kawashima O, Ishikawa S, Morishita Y. Sarcoid reactions in primary pulmonary carcinoma: report of seven cases. *Oncol Rep*. 1998;5(1): 177–80.
15. Steinfert DP, Irving LB. Sarcoidal reactions in regional lymph nodes of patients with non-small cell lung cancer: incidence and implications for minimally invasive staging with endobronchial ultrasound. *Lung Cancer*. 2009; 66(3): 305–8.
16. Brincker H. Sarcoid reactions in malignant tumours. *Cancer treatment reviews*. 1986; 13(3): 147–156.
17. Laurberg P. Sarcoid reactions in pulmonary neoplasms. *Scand J Respir Dis*. 1975; 56(1): 20–7.
18. Yamasawa H, Ishii Y, Kitamura S. Concurrence of sarcoidosis and lung cancer. *Respiration*. 2000; 67(1): 90–3.
19. Trisolini R, Cancellieri A, Patelli M. May sarcoidal reaction and malignant features coexist in regional lymph nodes of non-small cell lung cancer patients? *Lung Cancer*. 2009; 66(2): 272–3.

How to cite this article:

Demir OF, Onal O. Mediastinal Granulomatous Reaction in Lung Cancer in Capadocia Region. *J Clin Anal Med* 2017;8(6): 541–4.